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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,526	04/30/2001	Gary Maurice Dull	627-325IP	2781

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EXAMINER
BALASUBRAMANIAN, VENKATARAMAN

ART UNIT	PAPER NUMBER
1624	10

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,526	DULL ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,22-41,48-66 and 73-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 22-41, 48-66 and 73-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' response, which included amendment to claims 1-3, 16, 22, 25-27, 41, 48, 51-53, 66, and 73, filed on 8/12/2002, is made of record.

Claims 1-16, 22-41, 48-66 and 73-75 are pending.

In view of applicants' amendment, all 112 second paragraph rejections made in the previous office action have been obviated. However, in view additional search and further consideration, the following new rejections apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 22-41, 48-66 and 73-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Recitation of " Z_j''' is a non-hydrogen substituents" renders claim 1 and other dependent claims indefinite as this definition creates ambiguity as to what is Z_j'''. Note when j=0, Z_j''' is hydrogen. Appropriate correction is needed.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-66 and 73-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating treatment smoking addiction

and to improve brain function in dementia, associated with a dysfunction of nicotinic receptors, does not reasonably provide enablement for treatment of all or any diseases/disorders embraced in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use of the invention commensurate in scope with these claims.

The instant compounds are disclosed to have nicotinic receptor inhibitory activity and it is recited that the instant compounds are useful in treating several diseases, for which applicants provide no competent evidence. The disclosure in the instant case is not sufficient to enable the instantly claimed treatment of all CNS diseases and disorders solely based on the inhibitory activity disclosed for the compounds. Moreover many if not most of diseases of CNS such as Alzheimer's disease, multiple sclerosis, amylotrophic lateral sclerosis etc. are very difficult to treat and at present there is no known drug, which can successfully reverse the course of these diseases, despite the fact that there are many drugs, which can be used for modulating cholinergic function. That a single class of compounds can be used to treat all diseases embraced in the claims is an incredible finding for which applicants have not provided supporting evidence. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999)

wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the agonist activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Clementi et al. who expresses potential use of nicotinic receptor ligands for treating smoking addiction and to improve brain function in dementia. (Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements). Furthermore, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention:

The instant method of use claims are drawn to treatment of various diseases, /disorders due to dysfunction of nicotinic receptors including those yet to be discovered. However, specification provides no support for treating and or preventing all or any disorders. In fact based on the specification and examples

receptor binding, it appears that the instant compounds are mainly nicotinic receptor antagonist and may be useful for treating disorders wherein nicotinic receptor is implicated. Specification has not provided any evidence or nexus that because of the mode of action of the instant compound viz. nicotinic receptor antagonist, the compound would be useful for treating all or any disorders.

2) The state of the prior art:

There are no known compounds of similar structure, which have been demonstrated shown to be useful for treating all or any diseases. For example, the notion that a compound could be effective against all or any diseases because of its in interaction with a single target, in the instant case nicotinic receptor, in general is absolutely contrary to our current understanding of pharmacological basis of drug design and treatment of diseases. In fact a specific target is often chosen to treat a specific disease or that specific target related diseases. Furthermore, the prior art search in the related area does not suggest that because of the mode of action of a compound, as nicotinic receptor antagonist would be useful for all disorders. For example, Clementi et al. although discusses use of nicotinic receptor antagonist for treatment smocking addiction and to improve brain function in dementia, does not suggest use for prevention or treating all diseases/disorders embraced in the instant claims. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the

factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

3) The predictability or lack thereof in the art:

As noted above, although there several prior art which teach similar compounds as nicotinic receptor antagonist, they do not teach use of the compound disclosed for treating any or all disorders and hence there is no art predictability or assurance that instant compound would do so.

4) The amount of direction or guidance present:

Specification provides no guidance or direction, as to how would one use the instant compound to treat all or any disorder.

5) The presence or absence of working examples:

There are working examples to show that how the instant compound could be used to treat disorders wherein nicotinic receptor is implicated as causative agent.

6.The breadth of the claim:

The breadth of the claim is broad enough to include treatment of any or all diseases including those yet to be discovered for which there is no pharmacological basis or showing in the specification.

7) The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

This rejection is similar to the 112 rejection made in the previous office action. It appears examiner's suggestion was not clear. Specific diseases/disorders of dysfunction of nicotinic receptors was intended. Claims as recited includes any or all CNS diseases. Hence this rejection is applied again.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16, 22-23, 25-41, 48-66 and 73-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vernier et al. WO 99/32117.

Vernier et al. teaches several structurally similar compounds, which include generically those, claimed in the instant claims for the use as modulators of cholinergic receptors. See formula shown on page 6 and note the definition of A, B, D, E, G, J and R_1, R_2, R_3, R_4, and R_5. Note J corresponds to instant Q. See pages 6-47 for various preferred embodiments and process of making. See pages 47-70 for examples 1-35 for compounds made.

Instant claims differ from the reference in requiring pyridine compounds alkenylalkyl or akynylalkyl linked to Q groups. The reference teaches similar links but exemplifies those having hetero atoms as links between pyridine and Q groups.

However, Vernier et al teaches equivalency of the compounds of examples 1-35 with those generically defined and claimed in the definition of A, B, D, E, G, J and R_1, R_2, R_3, R_4, and R_5 of formula shown on page 6. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in pyridine ring, the side chain D, E, G and the hetero ring of J as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

This action is not made FINAL.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from

8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

10/30/2002